Type 2 Diabetes Pharmacotherapy

Treatment Algorithm for Glycemic Control (2024 Update)

References: American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1–S321. Individual FDA Prescribing Information labels.

Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy (metformin or other agents) should be selected based upon patient-specific factors *(e.g., glycemic goals, cardiorenal risk, comorbidities, cost and access)*.

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal.

Consider **early insulin initiation** with extreme hyperglycemia:
- BG ≥300 mg/dL
- A1C >10%
- Signs of catabolism

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Reassess treatment plan every **3-6 months** and modify if appropriate

Glycemic Treatment Goals

Treatment goals must be individualized (and periodically reassessed) after taking into consideration comorbid conditions, hypoglycemia risk, and other patient-specific characteristics.

POPULATION	A1C (%)	PREPRANDIAL	2-HR PPG
Most patients*	<7.0	80 - 130 mg/dL	<180 mg/dL
Certain patients**	<8.0	- -	- -

*More strict goals may be reasonable for certain patients, if achievable without significant hypoglycemia risk
**Risk of severe hypoglycemia, limited life expectancy, long duration of DM, prefer a less stringent A1C goal, etc.

Established/High-Risk of ASCVD, **Heart Failure**, or **Chronic Kidney Disease**? **No**

Recommended independent of baseline A1C, target A1C goal, or use of metformin

ASCVD
(established or high risk^)

GLP-1 RA or SGLT2i with proven CVD benefit

If A1C above target
- On GLP-1 RA? Consider use of SGLT2i with CVD benefit *(and vice versa)*
- Consider low dose TZD *(avoid in patients with HF)*

Heart Failure
(preserved or reduced EF)

SGLT2i† with HF benefit
- Avoid TZDs
- Avoid saxagliptin

If A1C above target

Chronic Kidney Disease
(eGFR < 60 mL/min and/or UACR ≥ 30 mg/g)

On maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with an eGFR as low as 20 mL/min
- Strongest evidence of benefit when UACR ≥ 200 mg/g
- If SGLT2i therapy is contraindicated or not tolerated, use of a **GLP-1 RA** with CVD benefit is recommended

If A1C above target

On SGLT2i? Consider use of GLP-1 RA *(and vice versa)*

^ **High-risk for ASCVD:** Typically age ≥ 55 years plus **two or more** risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)
† SGLT2i or SGLT1/2i with proven benefit in patients with heart failure (please note: sotagliflozin is not FDA-approved for glycemic control)

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin* • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) • empagliflozin (CKD) **Neutral:** • bexagliflozin* • ertugliflozin
Note: Sotagliflozin (SGLT1/2 inhibitor) is also a recommended option to provide heart failure benefit in patients with T2DM and heart failure. It is not approved for glycemic control.			
GLP-1 RAs & GLP-1/GIP RAs *GLP-1/GIP RA tirzepatide is under investigation for CV and renal benefit*	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

*FDA-approved in 2023; limited data suggests neutral cardiorenal effect.

NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 9/2023.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high** to **very high** glucose-lowering and weight-loss efficacy.

Glucose-Lowering Efficacy

Very High:
Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination therapy

High:
GLP-1 RA *(not listed above)*
Metformin
SGLT2i
Sulfonylurea
TZD

Intermediate:
DPP-4i

Weight-Loss Efficacy

Very High:
Semaglutide
Tirzepatide

High:
Dulaglutide
Liraglutide

Intermediate:
GLP-1 RA *(not listed above)*
SGLT2i

Intermediate:
DPP-4i
Metformin

Cost and Access

Consider oral options available in generic form or at a lower cost:
- SU or TZD*

**Only pioglitazone is available in a generic formulation*

Consider insulins that are available at lower cost:
- NPH or Regular

Please note: Insulin analogs (or inhaled insulin) are preferred to human insulins due to the lower hypoglycemia risk

Patient assistance programs may be available for certain brand name medications

If A1C above target

Add additional agents based on patient-specific factors including: glycemic goals, cardiorenal risk, comorbidities, cost and access

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GLP-1/GIP RA)

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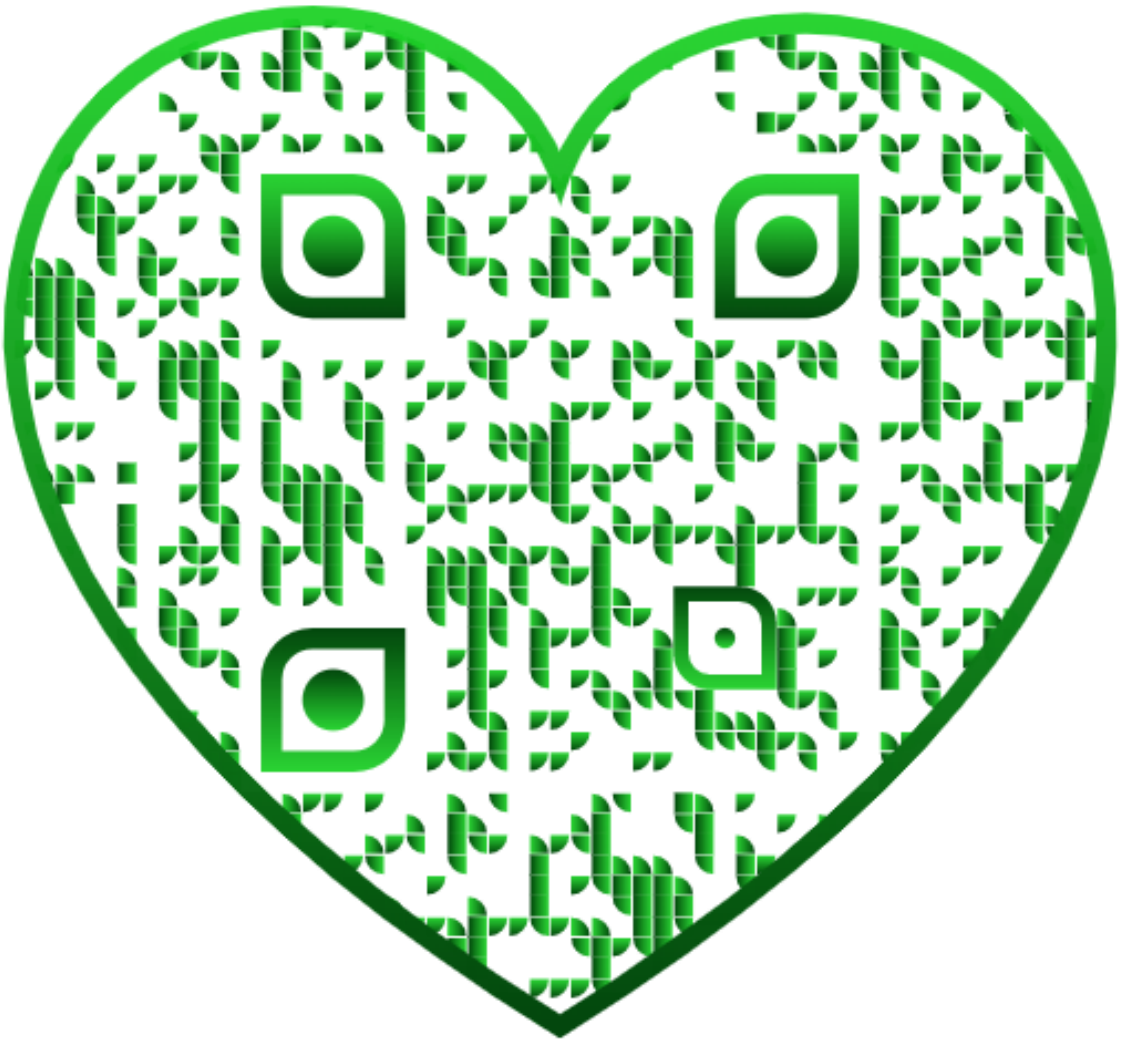

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Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy

Consider **early insulin initiation** with extreme hyperglycemia: BG ≥300 mg/dL, or A1C >10% or signs of catabolism present

→ **See Page 1** regarding non-insulin initial pharmacotherapy use and selection

Reassess treatment plan every **3-6 months** and modify if appropriate

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Injectable therapy needed to lower A1C?

Consider **GLP-1 RA** or **GLP-1/GIP RA** in most patients prior to insulin

Titrate to **maintenance dose**

Already on **GLP-1 RA** or **GLP-1/GIP RA**?
GLP-1 RA or GLP-1/GIP RA **not appropriate**?
Or is **insulin preferred**?

Assess basal insulin dose adequacy & evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:
- Basal dose > ~0.5 units/kg/day
- Elevated bedtime-morning/ post-preprandial differential
- Hypoglycemia (aware/unaware)
- High glycemic variability

Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors (e.g., cost)

START: 10 units/day or 0.1-0.2 units/kg/day

TITRATE to fasting plasma glucose (FPG) target:
- Follow an evidence-based titration algorithm, e.g., ↑ 2 units every 3 days until FPG target
- Hypoglycemia is never acceptable; titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, ↓ dose 10-20%

If A1C is above target

On bedtime NPH? Consider conversion to BID NPH

One possible approach:

START:
- Total dose = 80% of current
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

Based on individual's needs

If A1C is above target

Add prandial insulin

Usually start with one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

START:
- 4 units/day or 10% of basal insulin dose
- If A1C <8%, consider ↓ basal dose by 4 units/day or by 10% of basal dose

TITRATION:
- ↑ dose 1-2 units or 10-15% twice weekly
- If hypoglycemia occurs for no clear reason, ↓ dose by 10-20%

If A1C is above target

Consider BID premix insulin

START:
- Usually unit per unit at the same total insulin dose, but may require adjustment for the individual's needs

TITRATION:

Based on individual's needs

Stepwise additional prandial injections

(i.e. 1 then 2 then 3 injections daily)

Full basal-bolus regimen

(i.e. prandial insulin w/ meals and basal insulin)

Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

START:
- Total NPH dose = 80% of current NPH
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate components of the regimen based on the individual's needs

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